TRAUMA ORGAN PROTECTION WITH ARTESUNATE (TOP-ART): PRECLINICAL EFFICACY OF AN ANTIMALARIAL DRUG WITH EXCELLENT SAFETY PROFILE AND PLANNED PHASE II RCT.

HEM-3:

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Abstract

INTRODUCTION: Hemorrhagic shock (HS) is a common cause of death in severely injured patients and is associated with impairment of organ perfusion, systemic inflammatory response and multiple organ failure. The aim of the present study was to evaluate the effects of artesunate, the drug of choice for the treatment of falciparum malaria, on organ injury and dysfunction associated with HS in the rat.

METHODS: Rats were subjected to HS. The arterial pressure was reduced to 30 mmHg for 90min, followed by resuscitation with shed blood over 5min. Rats were treated with artesunate (2.4 or 4.8mg/kg; i.v.) or vehicle upon resuscitation. Four hours later, organ injury and dysfunction and the signalling events involved in the observed protective effects of artesunate were investigated.

RESULTS: HS resulted in a significant decrease in creatinine clearance, as well as rises in serum creatinine, aspartate aminotransferase, alanine aminotransferase and lactate, indicating the development of renal dysfunction, liver and muscular injury and organ ischemia. HS also caused significant increases in lung myeloperoxidase activity, NF-kappaB activation, iNOS expression and pro-inflammatory cytokines formation. Treatment of HS-rats with artesunate protected animals against the organ injury and dysfunction. Artesunate increased the activation of Akt and eNOS, inhibited the activation of GSK-3beta and NF-kappaB activation, and attenuated the increase in serum TNF-alpha and IL-6 associated with HS.

CONCLUSION: A single-centre placebo-controlled randomized phase II clinical trial will be conducted at Barts Health NHS Trust (TOP-ART) in late 2015 to evaluate the effects of GMP-artesunate in patients with severe hemorrhage following trauma.

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